White matter abnormalities of the motor network in schizophrenia

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Schizophrenia is a disease characterized by perception, cognition and also motor dysfunctions. These motor abnormalities are independent on antipsychotic medication and are called **soft neurological signs (SNS)**; they comprise above all mild coordination and sequencing of multiple motor schemes disorders. It is believed that these malfunctions are caused by defective coordination of cortical and subcortical functional areas [1].

Diffusion tensor imaging (DTI) is a relatively new technique based on magnetic resonance (MR), capable of depicting structural details of the brain white matter [2,3]. DTI parameters, especially fractional anisotropy (FA), have been described as disclosing subtle pathological changes in white matter integrity [2,4]. Several reports refer to significant changes of DTI parameters within the brain white matter in various pathologic conditions including schizophrenia [5,6,7].

In this paper we present pilot data of a study aimed at investigating the SNS pathogenesis, focusing on eventual **white matter abnormalities**. We employ the potential of combining two advanced neuro-imaging methods - DTI tractography and functional MR imaging (fMRI) to study specifically the pathologic changes of the motor system. The main objective of the study is to identify the white matter abnormalities within the motor network in patients with schizophrenia by the means of DTI data analysis.
Methods and Materials

The study group included **18 patients with schizophrenia** and **18 age-matched healthy volunteers** (median age 27 years, range 17-47 years). All of the patients underwent clinical examination evaluating motor abnormalities using standard neurological evaluation scale (NES). The average score for the group of patients was 3.6 ± 2.3. No abnormalities were found in the group of healthy volunteers.

All of the patients and controls were examined on a **1.5T MR scanner**. The study protocol included standard sequences for morphologic evaluation (T2 TSE and T1 3D gradient echo) and **DTI sequence** using b factor 1000 mT/s, 32 repeated acquisitions with different gradient vector orientation, isotropic voxel size 2mm. In the case of 8 subjects (4 patients and 4 controls) we performed also fMRI using motor task of sequenced hand movement; the block-paradigm consisted of 4 active and 4 rest periods lasting 30 seconds. During the active part of the examination the patients were asked to press the buttons of the MR-compatible keyboard repeatedly by their four right hand fingers in a specific order (2,4,3,5); visual presentation of the instructions was used. The response of the keyboard was registered by the PC used for the stimulation. **Table 1** shows detailed technical parameters of the imaging protocol.

**Table 1. MR imaging protocol parameters**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Slice thickness</th>
<th>Orientation</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>Flip angle</th>
<th>Acquisition matrix (mm)</th>
<th>Acquisition voxel size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 TSE</td>
<td>5</td>
<td>axial</td>
<td>shortest</td>
<td>100</td>
<td>90</td>
<td>384 x 240</td>
<td>0.6 x 0.77 x 5</td>
</tr>
<tr>
<td>T1 3D FFE</td>
<td>-</td>
<td>axial</td>
<td>25</td>
<td>shortest</td>
<td>30</td>
<td>300 x 235</td>
<td>0.9 x 0.9 x 1.6</td>
</tr>
<tr>
<td>DTI EPI SSh</td>
<td>2</td>
<td>axial</td>
<td>shortest</td>
<td>62</td>
<td>90</td>
<td>112 x 112</td>
<td>2 x 2 x 2</td>
</tr>
<tr>
<td>fMRI T2FFE</td>
<td>3.7</td>
<td>axial</td>
<td>3000</td>
<td>50</td>
<td>90</td>
<td>68 x 65</td>
<td>3.35 x 3.5 x 3.7</td>
</tr>
</tbody>
</table>

**Legend:** TSE - turbo spin echo, FFE - fast field echo, EPI - echo-planar imaging, SSh - single shot, fMRI - functional MR imaging, DTI - diffusion tensor imaging, TR - repetition time, TE - echo time.

The principal **analysis of the DTI data** comprised voxel-wise comparison of the DTI parameters between patients and controls. For the whole processing of the diffusion data
we used the FSL software platform (rel. 4.1, FMRIB, Oxford, UK) [8,9]. After the motion and eddy current co-registration of the source diffusion data, the FA images in all subjects were calculated. This data was used for tract-based spatial statistics (TBSS), which represents a novel approach for the diffusion data registration and analysis [10]. Finally we performed voxelwise statistical comparison (two-group unpaired t-test) of the FA and mean diffusion (MD) images between the group of patients and healthy subjects using Randomise utility (part of the FSL).

For single-level analysis of the fMRI data we used general linear model implemented in SPM5 software, the activation maps were generated (fig. 1). The activations were observed in three main areas associated with motor functions: left precentral gyrus, left supplementary motor area and right cerebellar hemisphere. In these areas we searched for the most significant voxels within the activated clusters.

For the visualization of the white matter motor connections we performed probabilistic tractography using ProbtrackX software (FSL). Probabilistic tractography is a relatively novel approach to depicting white matter tracts that avoids the need for multiple deterministic decisions at every step of the fibre-tracking process and allows us to trace beyond regions of low diffusion anisotropy deep into grey matter structures. The results are given as a probability of connection between specified brain regions [11]. We used three spheres with 5mm diameter localized at the fMRI maximal activation sites as a seed mask for tractography (fig. 2). The individual tractography data were analyzed by one sample t-test (Randomize, FSL) to create the mean image of motor system white matter tracts.
Images for this section:

**Fig. 0:** fMRI activation map in a healthy volunteer. Activation during motor-sequencing paradigm (movement of the right-hand fingers) is localized mainly in the left precentral gyrus, left prefrontal cortex and SMA (red).

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**Fig. 0:** Probabilistic tractography in an individual patient. Tract network connecting the left primary motor cortex, left SMA and right cerebellum is shown in red-yellow. The
white spots represent seed spheres centred at the sites of maximal fMRI activations and combined into a single mask.
Results

We found areas of significantly decreased FA values (p<0.05) including left frontal and parietal white matter and rostral callous body within the group of patients compared to healthy controls by means of TBSS analysis (fig. 1).

The group results of probabilistic tractography provided us with the image of mean tract network related to the fMRI activated areas. Furthermore, we created a binary mask from this data thresholded at p<0.05 and applied it to the TBSS results described above. By doing so, we localized the area of significantly decreased FA values within the left frontoparietal white matter in the group of patients compared to healthy volunteers (fig. 2).

In the group of patients we also observed an increase of the MD values within the frontal lobe white matter bilaterally (with left side predominance) compared to volunteers, nearly reaching arbitrary statistical significance (p=0.06) (fig. 3).
Images for this section:

**Fig. 0:** Voxelwise comparison of FA values between patients and healthy controls using TBSS. Four axial images of the brain using standard T1 MNI template with overlay of the mean skeleton of the white matter tracts (green). Red-yellow color represent areas with significantly decreased FA values of the white matter within the group of patients (p<0.05, corrected for multiple comparisons).

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Fig. 0: Masking the results of TBSS analysis (shown in Fig. 1) with the thresholded group data of tractography. Green - mean skeleton. blue - mean image of motor system white matter tracts thresholded at p#0.05. red-yellow - areas of significantly decreased FA values within the tractography mask in schizophrenic patients compared to healthy controls.

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**Fig. 0:** TBSS comparison of MD values between patients and healthy controls using TBSS. Areas of increased mean diffusivity values (blue color) using threshold p<0.06.

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Conclusion

The diagnostics of schizophrenia represents a challenge for current imaging modalities. Conventional MR examination as the top of the brain imaging quality does not usually prove any structural brain pathology, when classical visual evaluation is used. For the detection of subtle changes it is necessary to use more sophisticated methods of the image processing.

In the field of schizophrenia research several studies exhibit the brain white matter abnormalities using DTI. The fractional anisotropy changes of the white matter were detected, especially within association tracts connecting frontal, temporal and parietal cortex along with cingulum or corpus callosum [12,13].

In our study we focus on the neurological abnormalities associated with schizophrenia called soft neurological signs, SNS. Several authors have studied the structural background of cognitive deficit in patients with schizophrenia, but there have been only sparse references about abnormal imaging findings associated with neurological abnormalities. Previous studies using fMRI and positron emission tomography (PET) indicate diminished activation of sensory-motor cortex and supplementary motor area as possible pathophysiologic background of SNS [14,15]. However the exact pathogenesis, conceptual and neuroanatomical correlates of this event still remain unclear [16].

In agreement with previous studies we found several areas of significantly decreased FA values localized in the left frontal and parietal white matter and rostral corpus callosum in schizophrenic patients compared to the group of healthy controls. By combining the fMRI and DTI - probabilistic tractography we were able to focus on the areas of the white matter related specifically to motor system. Thus we identified area of significantly decreased FA values of the frontoparietal white matter within the motor network in patients with schizophrenia compared to healthy controls.

These results lead us to the conclusion that the white matter abnormalities may play an important role in the pathogenesis of SNS in schizophrenia.
References


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